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| 09/369,941 | 08/06/1999 | CHARLOTTE A. KENSIL | 106941.181 | 7453 |

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| ART UNIT | PAPER NUMBER |
| 1632 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/369,941 | KENSIL, CHARLOTTE A. | |
| | Examiner | Art Unit | |
| | Michael C. Wilson | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *64,67,68,70,72,74,76,90,92-103,105-114,127 and 128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,67,68,70,72,74,76,90,92-103,105-114,127 and 128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-13-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's arguments filed 12-13-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-18, 20, 29-62, 79-89, 91, 104, 115-126 and 129-149 have been canceled. Claims 19, 21-28, 63-78, 90, 92-103, 105-114, 127 and 128 are pending and under consideration in the instant office action.

### *Election/Restrictions*

Claims 19, 21-28, 63-78, 90, 92-103, 105-114, 127 and 128 are under consideration in the instant office action as they relate to a composition comprising a) saponin and b) an immunostimulatory oligonucleotide, and to a method of using such a composition (Group II). The claims are not being examined as they relate to a composition comprising a) saponin, b) an immunostimulatory oligonucleotide, and c) an antigen, or methods of using such a composition. For examination purposes a "nucleic acid sequence encoding an antigen" is not an antigen because antigens are proteins, and because nucleic acid sequences are materially distinct and separate than proteins.

### *Claim Objections*

The term "groups" in claims 109 should be –group--.

***Claim Rejections - 35 USC 112***

I. Claims 64, 67, 68, 70, 72, 74, 76, 90, 92-103, 105-114, 127 and 128 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The rejection of claims 64, 67, 68, 70, 72, 74, 76, 90, 103 and 127 regarding new matter (administering a saponin; an immunostimulatory oligonucleotide; and a nucleic acid molecule encoding an antigen) has been withdrawn.

Pg 10, lines 10-12 describes "immune adjuvant" but does not describe administering nucleic acids, specifically administering nucleic acids separately from the immune adjuvant.

Pg 12, lines 8-12, refer to increasing an immune response to antigen by administering a saponin adjuvant and an oligonucleotide. Pg 12, lines 8-12, does not describe administering nucleic acids, specifically administering nucleic acids encoding antigens, more specifically administering nucleic acids encoding antigens separately from the immune adjuvant.

Pg 14, line 22, to pg 15, line 2, describes target antigens, "antigens suitable for the enhanced immune response" (pg 14, line 17). Pg 14, line 22, to pg 15, line 2, states

the antigen may include a nucleic acid encoding the antigenic protein or peptide of interest (pg 15, lines 1-2).

Pg 15, lines 5-7, describes a vaccine comprising a saponin adjuvant, an immunostimulatory oligonucleotide, and an antigen.

Pg 16, lines 12-15, describe stimulating immunity to an antigen by administering a vaccine comprising an antigen, a saponin adjuvant and an immunostimulatory oligonucleotide.

Pg 18, lines 9-11, describes administering a composition "as a single injection of a mixed formulation of saponin, oligonucleotide, and antigen or as separate injections given at the same site with a short period of time".

While pg 14, line 22, to pg 15, line 2, does not describe administering nucleic acids to patients, pg 15, lines 5-7, states "[a]ccordingly, in a third aspect, the invention also encompasses a vaccine composition comprising a saponin adjuvant, an immunostimulatory oligonucleotide, and an antigen." It is readily apparent that the antigen in the vaccine on pg 15, lines 5-7, includes the nucleic acid sequence encoding an antigen described on pg 15, lines 1-2, because the paragraph on pg 15, line 5, begins with the word "accordingly." The use of the term "accordingly" connects the concepts in these two paragraphs and makes it clear that the antigen in the vaccine may be a nucleic acid encoding an antigen. It follows that the fourth aspect of the invention described on pg 16, lines 12-15, referring to a method of stimulating immunity

to an antigen in an individual using a vaccine comprising an antigen, a saponin adjuvant and an immunostimulatory oligonucleotide also is connected to the concept of the vaccine in the preceding paragraph beginning on pg 15, line 5.

The specification does not have to disclose *ipsis verbis* what is being claimed.

Claims 113 and 127 remain rejected because the phrase "wherein the nucleic acid comprising a nucleotide sequence encoding the antigen is administered to the individual within 2 days of said administering of the immune adjuvant" remains new matter. Pg 18, line 9, contemplates administering the composition as a "single injection of a mixed formulation of saponin, oligonucleotide, and antigen or as separate injections given at the same site within a short period of time (i.e. 0-2 days)." One of skill cannot extrapolate administering A and B+C separately as claimed from the description on pg 18, line 9, which appears to be limited to delivering A+B+C together or delivering A, B and C "as separate injections", i.e. each one by themselves.

Applicants repeat the argument that the specification reasonably conveys to those of skill that applicants had possession of the species claimed (i.e. administering A and B+C separately within 0-2 days (¶ bridging pg 13-14 of response filed 12-13-04). Applicants argue four possible combinations exist in the description on pg 18, lines 9-11. "Thus, the four possibilities for separate administration are: (1) administer saponin, oligonucleotide, and antigen separately (A+B+C, A+C+B; B+A+U; B+C+A; C+A+B; and C+B+A); (2) administer saponin and oligonucleotide together, antigen separately

(AB+C; C+AB); (3) administer saponin and antigen together, oligonucleotide separately (AC+B; B+AC); and (4) administer oligonucleotide and antigen together, saponin separately (BC+A; A+BC)." Applicants conclude, "[t]his is an extremely small genus, and, in the case of a limited genus, each member is adequately described without specifically naming each species, and that one of skill would have reasonably concluded that applicants had considered all four combinations including the one claimed." Applicants' argument is not persuasive.

First, and most importantly, pg 18, lines 9-11, appears to be limited to delivering A+B+C together, or delivering A, B and C "as separate injections". Nowhere does the specification imply (2) administering saponin and oligonucleotide together, antigen separately (AB+C; C+AB); (3) administering saponin and antigen together, oligonucleotide separately (AC+B; B+AC); or (4) administering oligonucleotide and antigen together, saponin separately (BC+A; A+BC). Applicants have not addressed this aspect of the rejection.

Assuming pg 18, lines 9-11, encompasses any combination of injecting A, B and C separately within 0-2 days, the three components may be injected as follows:

ABC together

A+B+C

A+C+B

B+A+U

B+C+A

C+A+B

C+B+A

AB+C

C+AB

AC+B

B+AC

BC+A and

A+BC

Applicants' arguments clearly set forth these 13 combinations within the "four combinations." The number of species within the genus then grows exponentially greater than 13 when varying the time between injections, i.e. 0-2 days. Thus, the species of administering saponin and oligonucleotide together, antigen separately (AB+C; C+AB) within a period of 2 days is not readily apparent from the vast number of species within the genus of administering saponin, oligonucleotide and antigen as separate injections within 0-2 days described in the specification.

The rejection of claims 121, 126, 131 and 134 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention regarding the phrase "such as" has been withdrawn because the claims have been canceled.

***Claim Rejections - 35 USC 103***

II. Claims 19, 21-27, 63-68, 73-77, 90, 95-98, 100-102, 113, 114, 127 and 128 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55) for reasons of record.

Weiner taught administering phosphorothioated oligonucleotide 1643 increased the humoral immune response in a mouse (page 10834, col. 1). 1643 has three unmethylated CpG motifs (pg 10834, Table 1; note the "ACGC" "TCGA" and "TCGA" = claim 27; pg 10833, col. 2, 11 lines from the bottom). Weiner did not teach combining 1643 with QS-7, -17, -18 or -21. However, at the time of filing, Kensil taught combining QS-7, -17, -18 or -21 with vaccines for an adjuvant effect (pg 23) and with other adjuvants to increase the adjuvant effect (pg 6, 2nd full ¶).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1643 of Weiner with QS-7, -17, -18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward

compositions with adjuvants that increased the humoral immune response and 2) 1643 and QS-7, -17, -18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the humoral immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1643 and QS-7, -17, -18 or -21 to increase the humoral immune response.

Applicants have generically argued the obviousness rejections together. The arguments have been addressed below. Future arguments to this rejection should be limited to evidence of synergy for oligonucloetide 1643 and QS-7, -17, -18 or –21. If applicants intend to write an appeal brief, each rejection must be argued separately to go to the board. The arguments for one obviousness rejection may refer to other obviousness arguments and may repeat the arguments. However, an appeal brief in which the three obviousness rejections are argued together will be considered defective.

III. Claims 19, 21, 24, 25, 27, 28, 65, 67, 69, 70, 73-77, 90, 95-98, 100-102, 113, 114, 127 and 128 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pg 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pg 1-55) for reasons of record.

Weiner taught administering oligonucleotide 1758 increased the humoral immune response in a mouse (pg 10834, col. 1) that has unmethylated CpG motifs and is equivalent to SEQ ID NO:1. 1758 is phosphorothioated (pg 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner did not teach combining 1758 with Quil A. However, at the time of filing, Kensil taught combining Quil A with other adjuvants to increase the adjuvant effect (pg 6 and pg 23). Quil A is purified from *Quillaja saponaria,* is less purified than QS-7, 17, 18 or -21 and has less of an adjuvant effect than QS-7, 17, 18 or -21 (page 3, 5, 11 and Fig. 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1758 of Weiner with Quil A as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1758 and Quil A could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1758 and Quil A to increase the immune response.

Applicants have generically argued the obviousness rejections together. The arguments have been addressed below. Future arguments to this rejection should be limited to evidence of synergy for oligonucloetide 1758 and QS-7, -17, -18 or –21. If

applicants intend to write an appeal brief, each rejection must be argued separately to go to the board. The arguments for one obviousness rejection may refer to other obviousness arguments and may repeat the arguments. However, an appeal brief in which the three obviousness rejections are argued together will be considered defective.

IV. Claims 19, 21-27, 63-68, 71-78, 90, 95-98, 100-102, 113, 114, 127 and 128 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chu (Nov. 17, 1997, J. Exp. Med., Vol. 186, pg 1623-1631) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 13, No. 1 and 2, pg 1-55) for reasons of record.

Provisional application 60/095,913 did not teach oligonucleotide 1826 (SEQ ID NO:2).

The effective filing date for administering 1826 (SEQ ID NO:2) with saponin as claimed is 4-8-99, the filing date of provisional application 60/128,608.

Chu taught administering oligonucleotide 1826 or 1760 as an adjuvant increased the IgG2a immune response in a mouse (pg 1625, col. 2, Fig. 1A and 1D). 1826 and 1760 have unmethylated CpG motifs, and 1826 is equivalent to SEQ ID NO:2. 1826 and 1760 are phosphorothioated (page 1625, col. 1, Table 1). Chu did not teach combining 1826 or 1760 with Quil A, QS-7, -17, -18 or -21. However, Kensil taught

combining Quil A, QS-7, -17, -18 or -21 with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* and QS-7, 17, 18 and -21 are purified from a less pure formulation of saponin. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotides 1826 or 1760 of Chu with Quil A, QS-7, 17, 18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Chu and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to add oligonucleotide 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 to increase the IgG2a immune response.

Applicants have generically argued the obviousness rejections together. The arguments have been addressed below. Future arguments to this rejection should be limited to evidence of synergy for oligonucloetide 1826 or 1760 with QS-7, -17, -18 or –21. If applicants intend to write an appeal brief, each rejection must be argued separately to go to the board. The arguments for one obviousness rejection may refer to other obviousness arguments and may repeat the arguments. However, an appeal

brief in which the three obviousness rejections are argued together will be considered defective.

**Old arguments regarding unexpected results**

Applicants have argued the specification and Friede (WO 00/62800) show unexpected synergy between "saponins with immune adjuvant activity... ...derived from *Quillaja saponaria*" and "an immunostimulatory oligonucleotide comprising at least one unmethylated CpG". Applicants have argued the species of unexpected results shown in the specification and in Friede represents the genus of saponins and unmethylated CpGs claimed. Applicants' arguments were not persuasive for reasons of record.

1) Example 1 (pg 20) and Figure 1 of the instant application describe using 1758 (SEQ ID NO:1) described by Weiner.

In Figure 1, assuming the data at the Effector:target ratio of 25 from top to bottom are:

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 85,

10 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 81,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 80,

10 ug QS-21 = 74

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 34

50 ug phosphorothioated CpG 1758 = 4

10 ug phosphorothioated CpG 1758 = 0

1.25 ug QS-21 = 0,

using the values for QS-21 or 1758 alone the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 0 + 0

1.25 ug QS-21 + 50 ug 1758 = 0 + 4

10 ug QS-21 + 10 ug 1758 = 74 + 0

10 ug QS-21 + 50 ug 1758 = 74 + 4

The unexpected results are:

1.25 ug QS-21 + 10 ug 1758 because 34 is greater than 0 + 0; and

1.25 ug QS-21 + 50 ug 1758 because 85 is greater than 0 + 4.

10 ug QS-21 + 10 ug 1758 is an expected result because 80 is not significantly different than 74 + 0 statistically; and

10 ug QS-21 + 50 ug 1758 is an expected result because 81 is not significantly different than 74 + 4 statistically.

Unexpected results in Example 1, Fig. 1 of the instant application do not represent the genus of saponin and CpG oligonucleotide claimed because some species within the genus cause expected results.

2) Example 4 (pg 22-23) and Figure 5 of the instant application describe using 1826 (SEQ ID NO:2) described by Chu.

In Figure 5, assuming

1.25 ug QS-21 = 52,

10 ug QS-21 = 93,

10 ug 1826 = 87,

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 46,

10 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 986,

using the values for QS-21 or 1826 alone the expected values would be:

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 52 + 87,

10 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 93 + 87.

The unexpected result is:

10 ug QS-21 + 10 ug phosphorothioated 1826 because 986 is greater than 93 + 87.

1.25 ug QS-21 + 10 ug phosphorothioated 1826 shows antagonistic result because 46 less than the expected value (52 + 87).

The unexpected results in Example 4, Fig. 5 for the species of 10 ug QS-21 + 10 ug phosphorothioated 1826 in the instant application do not correlate to the entire genus of saponin and CpG oligonucleotide claimed because Fig. 5 shows another species within the genus claimed that caused an antagonistic effect. The limited unexpected value obtained in Example 4 is not representative of the genus claimed.

3) Example 1 (pg 23-25) of Friede (WO 00/62800) appears to describe using 1826 (SEQ ID NO:2) described by Chu because Friede refers to the 1826 by Krieg. Krieg taught 1826 CpG was phosphorothioated.

In Fig. 1, assuming

20 ug 1826 = 750,

5 ug QS21 = 1250, and

20 ug 1826 + 5 ug QS-21 = 2200,

using the values for QS-21 or 1826 alone the expected values would be:

20 ug 1826 + 5 ug QS21 = 750 + 1250,

No unexpected results were obtained in Fig. 1 of Friede. The obtained result of 2200 was expected because 2200 is not significantly greater than 750 + 1250 statistically. Therefore, Fig. 1 of Friede does not support the argument of unexpected results.

b) In Example 1, Fig. 2, of Friede assuming

20 ug 1826 = 120,

5 ug QS21 = 180, and

20 ug 1826 + 5 ug QS-21 = 490,

using the values for QS-21 or 1826 alone the expected values would be:

20 ug 1826 + 5 ug QS21 = 120 + 180,

The obtained result of 490 was an unexpected result because 490 is greater than 120 + 180.

While Figure 2 of Friede shows unexpected results for the species of phosphorothioated 1826 and QS21 within the genus claimed, the results in Example 1, Fig. 2 of Friede do not represent the genus of saponin and CpG oligonucleotide claimed

because some species within the genus cause expected or antagonistic results as shown in Fig. 1 of Friede and Fig. 1 and 5 of the instant application.

4) Example 2 (pg 25-27) of Friede (WO 00/62800):

Fig. 3 shows unexpected results were obtained using 50 ug 2006 and 4.5 ug QS-21.

Fig. 4 shows two unexpected results were obtained using 50 ug 2006 and 4.5 ug QS-21 when A/Beijing and B/Panama were the targets and one expected result when A/Johann was the target (because the expected result (50 + 180) is not significantly greater than the obtained result (250)).

The tally:

9 unexpected results, 4 expected results and 1 antagonistic result.

Applicants have not taken into consideration the other Figures in the instant application.

5) Example 2 (pg 21) and Figure 2 of the instant application:

In Figure 2, assuming the values at the Effector:target ratio of 25 are:

No adj = 0,

2 ug CpG = 0,

10 ug CpG = 0,

50 ug CpG = 61,

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 0,

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 42,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 62,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 30,

1.25 ug QS-21 = 0, and

10 ug QS-21 = 36,

the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 0 + 0

1.25 ug QS-21 + 50 ug 1758 = 0 + 61

10 ug QS-21 + 10 ug 1758 = 36 + 0

10 ug QS-21 + 50 ug 1758 = 36 + 61

The unexpected result is:

10 ug QS-21 + 10 ug 1758 because 62 is greater than 36 + 0.

1.25 ug QS-21 + 10 ug 1758 is an expected result because 0 is not significantly different than 0 + 0 statistically

1.25 ug QS-21 + 50 ug 1758 is an antagonistic result because 42 is less than the expected 0 + 61; and

10 ug QS-21 + 50 ug 1758 is an antagonistic result because 30 is less than the expected 36 + 61.

6) Example 3 (pg 21) and Figure 3 of the instant application:

In Figure 3, assuming the values of IgG1 are:

10 ug CpG = 1000

50 ug CpG = 1000

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 5000,

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 20,000,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 110,000,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 100,000,

1.25 ug QS-21 = 1000, and

10 ug QS-21 = 100,000,

the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 1000 + 1000

1.25 ug QS-21 + 50 ug 1758 = 1000 + 1000

10 ug QS-21 + 10 ug 1758 = 100,000 + 1000

10 ug QS-21 + 50 ug 1758 = 100,000 + 1000

The unexpected results are:

1.25 ug QS-21 + 10 ug 1758 because 5000 is greater than 1000 + 1000.

1.25 ug QS-21 + 50 ug 1758 because 20,000 is greater than 1000 + 1000.

10 ug QS-21 + 10 ug 1758 is an expected result because 110,000 is the expected value.

10 ug QS-21 + 50 ug 1758 is an expected result because 100,000 is not significantly different than the expected 100,000 + 1000 statistically.

7) Antagonistic results were obtained in Fig. 4 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 74 which is much less than the expected 40+63. Fig. 4 showed unexpected results with 10 ug QS-21 + 10 ug CpG.

8) Antagonistic results were obtained in Fig. 6 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 76 which is less than the expected 12+71. Fig. 6 showed unexpected results with 10 ug QS-21 + 10 ug CpG.

9) Unexpected results were obtained in Fig. 7 of the instant application. 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 785 which is greater than the expected 14 +

19. 10 ug QS-21 + 10 ug CpG caused an IgG titer of 8454 which is greater than the expected 186 + 19.

10) Antagonistic results were obtained in Fig 8 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 239 which is much less than the expected 5+352. 10 ug QS-21 + 10 ug CpG caused an unexpected IgG titer of 44806 which is greater than the expected 94 + 352.

The tally in the specification:

13 unexpected results, 5 expected results and 6 antagonistic results.

The tally in the specification plus what was known in the art at the time of filing:

(this includes Friede Example 1, Fig. 1 and 2, which used oligonucleotide 1826 known in the art):

14 unexpected results, 6 expected results and 6 antagonistic results.

The tally in the specification plus what was known and unknown in the art at the time of filing within the genus claimed:

(this adds Friede Example 2, Fig. 3 and 4, which used oligonucleotide 2006 which was not described in the art at the time of filing):

19 unexpected results, 6 expected results and 7 antagonistic results.

No matter how one of skill would look at the data in the specification and Friede, the examples of saponin plus CpG that provided unexpected results are not representative of the genus claimed. The limited examples of unexpected synergy in the instant application and Friede cited by Dr. Kensil in the declaration in paragraph 5 do not support unexpected synergy for the genus claimed because many combinations within the genus only provided expected results and some provided less than expected results.

**New arguments regarding unexpected results**

Applicants now argue in the response filed 12-13-04 that the examiner's position is not the applicable standard of the law. Each CpG oliognucleotide showed unexpected results under some condition. Each CpG oligognucleotide need not show unexpected results at every data point (pg 16 of response filed 12-13-04). Applicants' arguments are not persuasive. In this case, the unexpected synergistic effects are so limited as compared to the expected effects and the unexpected inhibitory effects and cannot be used to overcome the genus of CpG oligonucleotide and saponin as broadly claimed. For example, the two unexpected antagonistic results and the one expected results for oligonucleotide 1758 outweigh the one unexpected result (see item 5) under the "Old arguments regarding unexpected results"; Example 2 (pg 21) and Figure 2 of the instant application). Applicants have not addressed the fact that some combinations

within the genus of oligonucleotide 1758 and saponin have an unexpected antagonistic effect.

Applicant's arguments on pg 18, lines 8-15, of the response filed 12-13-04, are persuasive. The data in Example 2 of Friede can be relied upon for post-filing evidence of synergy because while the specification does not provide adequate written description for CpG 2006, WO 98/18810 published May 7, 1998 described CpG 2006 on pg 19, line 18. Thus, the results described in Friede used a CpG oligonucleotide known in the art at the time of filing.

**Old arguments regarding CpGs acting in the same manner**

Applicants point to paragraph 6 of the declaration by Dr. Kensil, who states CpGs are expected to act in the same manner with respect to immune adjuvant activity. Applicants' argument is not persuasive. Fig. 3 and 4 of the instant application show two different CpGs (1758 and 1826) at 10 ug provide different IgG1 titers (1000 vs 63). In the case of 1758, 10 ug caused less antibody production than no adjuvant. Thus, one of ordinary skill would not conclude that all CpGs cause the same immune response and would not have been able to determine which CpG had an adjuvant effect or at what concentration such CpGs would provide synergy when combined with a saponin as claimed. Applicants' arguments regarding mechanism of action by which CpG "exert their activity through the same receptor" in paragraph 6 of the declaration and in the

paragraph bridging pg 24-25 of the response filed 4-26-04 are moot because the specification shows 1758 caused did not stimulate the immune response as compared to no adjuvant.

**New arguments regarding CpGs acting in the same manner**

Applicants argue the different IgG1 titers in Fig. 3 and 4 are from the difference between experimental systems. "Figure 3 shows the response to a T-dependent antigen (ovalbumin) in C57BL/6 mice after three immunizations. Many T-dependent antigens, such as ovalbumin, will typically have an IgG1 response in the absence of adjuvant because they contain T helper epitopes. Figure 4 shows a T-independent antigen in Balb/c mice and with only two immunizations. Applicant points out that magnitude of response will depend on the experimental system and antigen, and thus will vary, but this variation is not indicative of the fact that there is not a common immune adjuvant activity that is shared among CpG oligonucleotides as a genus." Applicant's argument is not persuasive because it does not address the extreme difference between an antibody of titer of 1000 vs 63 obtained using two different CpG oligonucleotides. Thus, Fig. 3 shows two different CpGs affect the ability to induce antibodies differently. Applicant's argument is also not persuasive because it ignores the fact that 10 ug of oligonucleotide 1758 caused less antibody production than no adjuvant. The examples in the specification clearly show different CpGs affect the immune system differently.

**Old arguments regarding QS-21 representing the genus of QS saponins**

Applicants argue QS saponins share structural similarities and that QS saponins in general are expected to exhibit a common immune adjuvant function (¶ 7-10 of the declaration and ¶ bridging pg 24-25 of the response filed 4-26-04). First, Dr. Kensil shows how QS-17, -18 and –21 share two structural features (¶ 8) and that other saponins share structural similarities (¶ 9). Dr. Kensil concludes that "[b]ecause of the structural similarity of the QS saponins and the correlation of structure with function, and the evidence that QS saponin QS-21 exhibits synergy in immune adjuvant activity with CpG oligonucleotides, I conclude that synergy in immune adjuvant activity is reasonable expected to be a general property of the genus of QS saponins" (¶ 11). Applicants' argument is not persuasive.

First, the conclusion in ¶ 11 of the declaration is flawed because applicants shown no functional similarity between QS-17, -18 and –21. No "correlation of structure with function" had been established for QS-17, -18 and –21 in the art at the time of filing or by applicants, especially in view of the varying data in Fig. 1-9 of the instant application. Second, Fig. 1 and 2 of the instant application shows 1.25 ug of QS-21 did not have an adjuvant activity, but 10 ug QS-21 did have adjuvant activity. Fig. 3 shows QS-21 causes an IgG1 effect but not an IgG2A effect. One of ordinary skill in the art would easily recognize that QS-21 does not always provide an immunostimulatory

effect. Given applicants' data, one of ordinary skill would conclude that QS-21 was capable of providing specific stimulate some aspects of the immune system and that the immunostimulatory effect were limited to certain concentrations. One of ordinary skill could not reasonably conclude that QS-21 would exhibit synergy in any immune activity as concluded by Dr. Kensil. Nor would one of ordinary skill have concluded that such synergy would occur for any immune response at any concentration. Therefore, the variable results in the specification and Friede when using QS-21 do not adequately correlate to any other saponins as claimed.

**New arguments regarding QS-21 representing the genus of QS saponins**

Applicant's arguments regarding Fig. 2 on pg 17, 2nd full ¶, are noted. Examples 1 and 2, Fig. 1 and 2, of the instant application showed 1.25 ug of QS-21 did not have adjuvant activity, while 10 ug QS-21 did have adjuvant activity. This has been fixed in the paragraph above.

**Other old arguments**

Applicants point to case law from In the Matter of the Application of Kollman, 595 F.2d48(C.C.P.A. 1979) in which "the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data" and that "one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." Applicants' argument is not

persuasive. In this case, the data clearly shows that one of ordinary skill would not have concluded that random examples of unexpected synergy within the genus of CpG and QS saponins as claimed were representative of the genus. One of skill would have recognized that many species within the genus claimed had an antagonistic or expected effect and would have concluded that synergy would be obtained only sometimes, and that it could not be determined when synergy would occur.

Applicants point to Application of Katzschmann, 347 F.2d 620 (CCPA 1965) which states, "[w]e do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skill in the art." In this case, the examiner has supported his position (that the examples of unexpected synergy in Fig. 1 and 5 of the instant application and Friede described in paragraph 5 of the declaration are not representative of the genus claimed) with applicants' own teachings. The examiner has used data and logic, not speculation, to support his position.

***Double Patenting***

The rejection of claim 126 under 37 CFR 1.75 as being a substantial duplicate of claim 121 has been withdrawn because claims 121 and 126 have been canceled.

The limitation of a CpG motif having the formula 5'$X_1$CG$X_2$3' in claim 27, 98 and 111 still cannot be searched because the nucleic acid is so small and may be part of any plasmid, which is very large in comparison, and cannot be adequately searched on computer databases or by eye.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

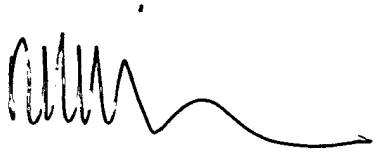
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER